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CASE REPORT

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# Anti-Programmed death-1 therapy in advanced hepatocellular carcinoma: A real-world experience

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**Abstract**

Nivolumab is an effective and safe treatment in HCC.

**KEYWORDS**

clinical outcomes, hepatocellular carcinoma, nivolumab, survival

## 1 | BACKGROUND

Hepatocellular carcinoma (HCC) ranks first among primary liver malignancies and represents the second cause of cancer-related death worldwide. Nivolumab has the FDA approval for advanced HCC. Our study aim is to assess the clinical and survival outcomes of patients with HCC who received nivolumab in the real world.

Hepatocellular carcinoma (HCC) ranks first among primary liver malignancies and represents the second cause of cancer-related death in East Asia and sub-Saharan Africa and the sixth most common in western countries.[1-3] The main well-recognized risk factor of HCC is cirrhosis with all its related etiologies and chronic viral infection by hepatitis B and C.[4]

The treatment options of HCC were expended by multiple molecular targeted agents' development, leading to its prognosis improvement. The first tyrosine kinase inhibitor (TKI) approved in HCC was sorafenib in 2007, which has improved survival outcomes by 2.3 to 2.8 months.[5,6] Recently, other TKIs were analyzed in clinical trials and became available in treating this aggressive cancer, such as regorafenib, lenvatinib, cabozantinib, and ramucirumab. Lenvatinib that inhibits angiogenesis and tumor proliferation was analyzed in REFLECT trial. This phase III trial demonstrated that lenvatinib might be considered as effective as sorafenib in OS outcomes in patients with not previously treated advanced HCC.[7] Moreover, the role of regorafenib, an oral multikinase inhibitor, in HCC management according to the data of phase III placebo-controlled RESORCE trial in patients resistant to sorafenib without arm was observed over the placebo arm.[8] Cabozantinib has also improved the OS outcomes by 2.2 months in HCC over the placebo, in a phase III trial (CELESTIAL trial) that included patients that progressed after at least one prior systemic treatment.[9] Similarly, the VEGF-R2 monoclonal antibody ramucirumab was tested in REACH-2 trial. The primary end point of this phase III study was met, confirming ramucirumab superiority after sorafenib progression, over the placebo in OS in HCC with alpha-fetoprotein concentrations of at least 400 ng/mL.[10]

Tumors might be able to evade the host immune surveillance if overexpressed immune checkpoints with

negative regulation of antitumoral immune response. The objective of blocking Immune checkpoint is to induce the reactivation of immune response and the destruction of malignant cells by tumor-specific T cells.[11] Immune cells such as B and T lymphocytes expressed the programmed death-1 (PD 1).[12] The PD-1 inhibitors fixed the receptors of PD-L1 and PD-L2, conducting to the stimulation of immune cells.[13] Notably, nivolumab is the first monoclonal antibody directed against PD in the world. The nivolumab was studied in Checkmate-040 trial that enrolled advanced HCC and highlighted a 20% response rate, with 2 complete responses and a 67% of disease control rate, and 9.9 months for the median response duration.[14] Nivolumab had the United States Food and Drug Administration (FDA) approval for HCC in 2017. However, the European Medicines Agency (EMA) approval has not yet been obtained. Recently, at the ESMO Congress 2019 in Spain, the results of phase III head-to-head trial (Checkmate-459 trial) comparing nivolumab to standard-of-care in first-line sorafenib were reported. In this trial, nivolumab did not achieve statistical significance for the primary end point, although better safety profile and OS outcome, with higher overall and complete response rates as were observed with nivolumab.[15]

In Europe, nivolumab is used if intolerance or progression under TKI treatment and no accessibility to other tumor-directed therapies. Our report from a real-world experience aims to evaluate the clinical benefit of nivolumab in patients with advanced HCC in a single oncology center.

## 2 | PATIENTS AND METHODS

This retrospective cohort enrolled 15 patients with confirmed metastatic HCC, treated by anti-PD1 at the Medical Oncology Department of Paul Brousse Hospital, France.

Demographic, laboratory, imaging, and outcome data were reviewed and analyzed. Diagnosis of HCC was established according to the international guidelines. Inclusion criterion was as follows: confirmed advanced HCC treated by nivolumab. The Barcelona-Clinic Liver Cancer (BCLC) stage was determined.[16] In addition, the Child-Pugh score was defined based on the Child-Pugh classification.[17]

ALBI grade was determined by the following formula: ([log10 bilirubin × 0.66] + [albumin × [−0.085]], where bilirubin is in μmol/L and albumin in g/L). ALBI grade was assigned to one of the 3 predescribed ranges: < 2.60 (ALBI 1), >2.60 to ≤ 1.39 (ALBI 2), and >1.39 (ALBI 3).[18]

PALBI grade was determined by the following equation: 2.02 × log10 bilirubin-0.37 × (log10 bilirubin)$^2$-0.04 × albumin-3.48 × log10 platelets + 1.01 × (log10 platelets)$^2$, bilirubin was expressed in μmol/L, albumin in g/L and blood platelet count in 1000/μL. PALBI grade was assigned into 3 ranges: ≤2.53 (PALBI 1), >2.53-2.09 (PALBI 2), and >2.09 (PALBI 3).[19]

Neutrophil, lymphocyte, and platelet counts were determined by the Coulter method. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated as the ratio of neutrophil cell and platelet count to lymphocyte cell count, respectively.

Committee approval and informed consent were not needed because the study was observational and retrospective. The study was conducted with absolute respect for international ethics standards (anonymity and data protection).

The Nivolumab administration followed the recommendations of official dosing and safety information. The radiological evaluation was programmed every 8-12 weeks during Nivolumab treatment. Responses to treatment were determined according to the Modified Response Evaluation Criteria in Solid Tumors Criteria 1.1 (mRECIST 1.1).[20] Overall response rate (ORR) was defined as the percentage of patients who had a partial or complete biologic and/or radiologic response to nivolumab. In addition, toxicity related to the treatment was graded based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[21]

In this study, we used OS and PFS as primary end points. OS was defined as the time from the initiation of nivolumab until either death from any cause or the date of last follow-up. PFS was determined as the length of time from the initiation of treatment by nivolumab to the date of the first signs of progressions confirmed by the investigator in the medical record, or the date of death or date of latest events when the patient is censored.

SPSS 22.0 software was used to perform the statistical analysis. Continuous variables were presented as means ± standard deviation, and categorical variables were reported as frequencies and percentages. Survival analyses were performed using Kaplan-Meier method for univariate analysis and multivariate analysis by Cox regression model. For all analysis, the p value statistically significant was < 5%.

## 3 | RESULTS

### 3.1 | Clinical-pathological characteristics

Fifteen patients were analyzed in our study. Among patients population, 11 were males (73.3%) and 4 were females (26.7%). The median age was 60 ± 8 years [48-83]. Chronic hepatitis was the predominant cause of HCC (60%). All patients presented with cirrhosis. The Child-Pugh stages were A (33.3%), B (46.7%), and C (20%), respectively. 60%

**TABLE 1** Baseline characteristics of the study population

| Characteristics | Number of patients (%), N = 15 |
|---|---|
| Age | |
| Median (Range) | 60 (48; 83) |
| Gender | |
| Male | 11 (73.3) |
| Female | 4 (26.7) |
| Etiology of cirrhosis | |
| Hepatitis B | 3 (20) |
| Hepatitis C | 6 (40) |
| Alcoholic | 2 (13.3) |
| NASH | 2 (13.3) |
| Others | 2 (13.4) |
| AFP | |
| Median (range) | 803 (3 - 7037) |
| ALBI | |
| Median (range) | -1.9 (−2.89; - 0.18) |
| ALBI grade | |
| 1 | 7 (46.7) |
| 2 | 5 (33.3) |
| 3 | 3 (20) |
| PALBI | |
| Median (range) | -1.76 (−3.21; - 0.76) |
| PALBI grade | |
| 1 | 6 (40) |
| 2 | 1 (6.7) |
| 3 | 8 (53.3) |
| NLR | |
| Median (range) | 3.4 (1.04; 22.8) |
| PLR | |
| Median (range) | 167 (52; 440) |
| BCLC stage | |
| A | 0 (0) |
| B | 6 (40) |
| C | 9 (60) |
| D | 0 (0) |
| Child-Pugh score | |
| A | 5 (33.3) |
| B | 7 (46.7) |
| C | 3 (20) |
| Extrahepatic metastasis | 10 (66.7) |
| ECOG | |
| 0 | 10 (66.7) |
| 1 | 4 (26.7) |
| 2 | 1 (6.6) |
| Previous treatment | |
| Surgery | 7 (46.7) |
| Locoregional | 8 (53.3) |
| Sorafenib | 15 (100) |
| Line of treatment by nivolumab | |
| 2nd | 1 (6.6) |
| 3rd | 7 (46.7) |
| 4th | 6 (40) |
| 5th | 1 (6.7) |
| Treatment duration of nivolumab | |
| Median (range) | 8 (4; 30) |
| Nivolumab's overall response rate (ORR) | 4 (26.7) |

patients carried BCLC stage B disease and 40% stage C. Table 1 summarizes patients, tumor, and treatment characteristics at baseline.

The median ALBI score was −1.9. Seven patients (46.7%) were ALBI grade 1, five patients (33.3%) were ALBI 2 and 20% were ALBI 3. The median PALBI score was – 1.76. 40% of patients were PALBI grade 1, 6.7% and 53.3¨% were PALBI 2 and PALBI 3, respectively. The median values of NLR and PLR were 3.4 and 167, respectively.

Seven patients (46.7%) have undergone initial curative surgery and 8 patients (53.3%) have received locoregional therapies including Selective Internal Radiotherapy (SIRT) in 2 cases and Transarterial chemoembolization (TACE) in 6 cases. The first systemic treatment received by all patients was sorafenib. The other therapeutic options used were tyrosine kinase inhibitors with antiangiogenic activity such as regorafenib, lenvatinib, and cabozantinib. 6.6% of patients received nivolumab in the 2nd line, 46.7% in the 3rd line, 40% in the 4th line, and 6.7% in the 5th line, respectively. The median nivolumab's duration treatment was 8 cycles (4-30). Concerning the bioradiological outcomes of Nivolumab treatment, 4 patients (26.7%) showed an AFP response with declining levels. The best radiological response was a partial response in 2 patients (13.3%) and stability in 2 other patients (13.3%). Eleven patients (73.3%) had progressive disease. Moreover, 2 patients (13.3%) developed grade 2 hypothyroidism, 2 patients (13.3%) had grade 2 asthenia and 1 patient (6.6%) had grade 1 hepatic cytolysis, which were the principal toxicity profile of nivolumab.

Ten patients (66.7%) were still alive after a median follow-up of 34 months (13 - 72). and five patients (33.3%) were died at the time of analysis.

### 3.2 | Survival outcomes

The median OS in the whole cohort was 10 months [6.6 - 13.3] and median PFS was 7 months [5.3 - 8.6].

The ALBI grade ($P$ =.028), PALBI grade ($P$ =.03), pre-treatment NLR > 3 ($P$ =.013), and PLR > 160 ($P$ =.017) were prognostic factors associated with PFS according to the Kaplan-Meier univariate analysis (Table 2).

The ALBI grade ($P$ =.04), PALBI grade ($P$ =.017), NLR > 3 ($P$ =.033), and serum alpha-fetoprotein ($P$ =.027) ≥ 800 ng /ml were significantly associated with OS. Only the high level of serum alpha-fetoprotein ≥ 800 ng /ml remained significantly independent factor of OS (HR: 7.2, CI 95% 1.8 - 65, $P$ =.043) in the multivariate analysis by Cox regression model. (Table 3).

## 4 | DISCUSSION

The chronically inflamed liver background favored the development of most HCC. These tumors are considered typical immunogenic cancers, escaping immune surveillance. The overexpression of PD-L1 and signaling pathway activation stimulated by the binding of PD-1 to its ligands are the two major mechanisms conducting to immune response reactivation.[22] In HCC tissues, PD-L1 expression might be higher.[23] Also, the most common pathogens of HCC are the hepatitis B (HBV) and hepatitis C (HCV) viruses-related infections that activated the immune system against viruses using the immune checkpoint pathways.[24] The restoration of T-cell function leading to the antitumor immune surveillance, with effective detection and destruction of the HCC tumor cells is the objective of the immune checkpoint blockade. Therefore, clinical trials testing PD-L1 inhibitors in HCC have been conducted.

Our study demonstrated an ORR of 26.7% with nivolumab which was similar to that observed in the Checkmate-040 trial.[14] Outcomes from 11 real-world patients that received nivolumab for HCC management were reported by a Chinese group. All patients had HBV-related cirrhosis and were BCLC stage B or C. The results of this trial were interesting with only 2 cases of progressive disease (18.2%).[24] A retrospective real-life experience of patients with HCC (BCLC stage B and C) treated by nivolumab in three Germen university hospitals have shown a clinical activity of nivolumab with a median OS of 7.5 weeks (range 0 - 46) and ORR of 35.3%.[25] Our results and also those reported in the literature confirmed that nivolumab could be safe and efficacious in liver cancer management.[24,25] Despite the high cost of nivolumab, it has demonstrated substantial antitumor activity and favorable toxicity profile as salvage treatment of HCC in our study. Therefore, there is a need to assess its value by considering both efficacy and cost.

**TABLE 2** Univariate analysis of significant factors associated with PFS

| Parameters | Univariate analysis *P*-value |
|---|---|
| ALBI grade | .028 |
| PALBI grade | .03 |
| NLR > 3 | .013 |
| PLR > 160 | .017 |

Our study aim is to analyze and determine the prognostic factors influencing OS and PFS. There were some studies analyzing the interest of ALBI and PALBI grades in HCC inaccessible to locoregional treatments.[26] A recent study published in 2017 found that the predictive value of both ALBI and PALBI is higher as compared to the Child-Pugh score in patients with HCC treated by invasive therapies. ALBI and PALBI may be useful for selecting patients more likely to survive under treatment by Nivolumab, according to our study.[27] The ability prognostic of these scores and their role as a useful tool to improve risk stratification in HCC patients in clinical practice were suggested, although, the confirmation of these results in larger scale prospective studies are warranted.

The inflammation was a main factor leading to cancer progression.[28] Recently, many studies have focused on hematological parameters, which can reflect the status of immune responses in cancer patient.[29,30] NLR and PLR are predictive factors of survival in cancer, probably as biomarkers of systemic inflammation, but with limited evidence in HCC. Our cohort showed that NLR and PLR seemed to be useful tool to predict survival in HCC patients. However, to evaluate the prognostic ability of these blood-based biomarkers as predictors of outcomes in this setting, further studies are needed.

Approximately 70% of HCC secreted the alpha-fetoprotein (AFP). This glycoprotein is used in screening and diagnoses in multiple reports.[31] Recently, the AFP response was unanimously suggested as a prognostic tool for OS in HCC patients after locoregional treatment or systematic chemotherapy in several studies.[32,33] In our cohort, we demonstrated that serum alpha-fetoprotein ≥800 ng/mL predicted poorer OS (HR: 7.2, 95% CI: 1.8 - 65, $P$ =.043). In order to improve its accuracy as a predictive biomarker for HCC staging, cohorts with a larger enrollment are needed.

Finally, the retrospective and single-center characteristic of our case series as well as the small sample size are the major limitations of our findings.

## 5 | CONCLUSION

Nivolumab therapy demonstrated promising efficacy and manageable toxicity in HCC patients. The serum

**TABLE 3** Univariate and multivariate analysis of significant factors associated with OS

| Parameters | Univariate analysis *P* value | Multivariate analysis HR | 95% CI | *P* value |
|---|---|---|---|---|
| ALBI grade | .04 | | | |
| PALBI grade | .017 | | | |
| NLR > 3 | .033 | | | |
| AFP ≥ 800 ng/mL | .027 | 7.2 | [1.8 - 65] | 0.043 |

alpha-fetoprotein level ≥800 ng/mL was a statistically significant prognostic factor for OS. Further studies analyzing the interest of immune checkpoint blockade in HCC are awaited to confirm these findings.

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## CONFLICT OF INTEREST

None declared.

## AUTHOR CONTRIBUTIONS

OA: conducted the study and wrote the manuscript under the supervision of Prof JFM. HC: assisted in writing and editing the manuscript. AU: participated in patient's management. WA: participated in patient's management. YG: participated in patient's management. EG: participated in patient's management. SA: contributed in the draft revision.

## ETHICS STATEMENT

Ethics committee was not required given the retrospective nature of this study retrospectively. However, patients' consent for publication was obtained verbally.

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